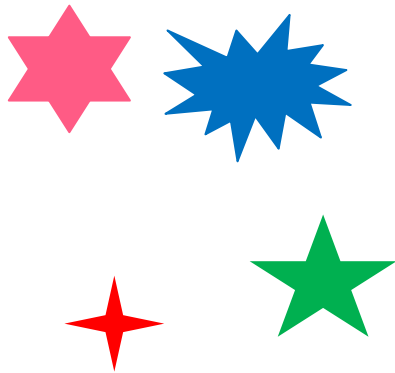


Development of Control Strategy for Vaccine Products

Cristiana Campa
GSK Vaccines, Technical R&D

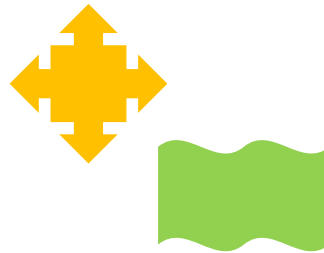
WCBP, January 2018

Antigen(s)



- Typically, complex and multiple antigens with different structural features and doses
- Needed for **specificity of the immune response**

Adjuvant



- Aluminum salts or Adjuvant Systems (combination of immunostimulatory molecules).
- Needed for most of the inactivated (whole or subunit) vaccines to **enhance and modulate immunogenicity of the vaccine antigen**



Administered Vaccine



- All components in an appropriate buffer
- May require reconstitution/ mixing of different component solutions before administration
- Typically filled in vial or syringe, depending on formulation composition and patient needs

Vaccines development

Points to consider



Complexity of products and processes, and consequent challenging and difficult characterization

Wide variety of possible vaccine categories/ structural features, implying relatively limited possibility to leverage information from different product types

Analytical strategy able to detect structural and formulation changes and their impact on immunogenicity for highly complex products

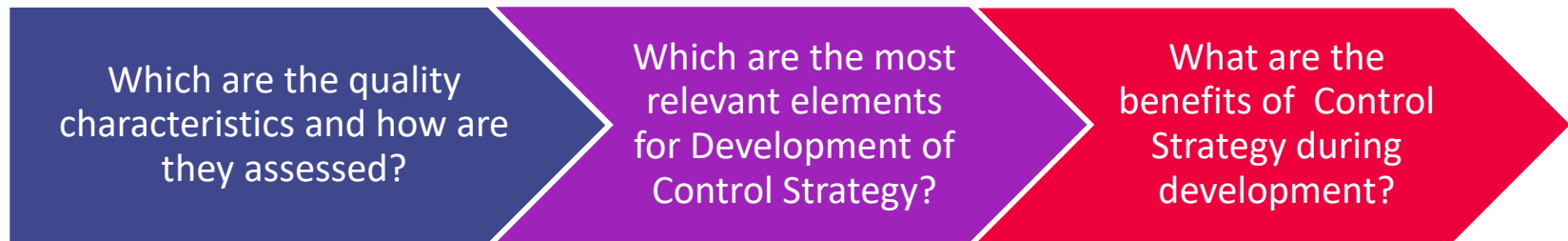
Knowledge of antigen structure, formulation, analytics and process are instrumental for attribute selection and definition of attribute ranges to be clinically explored

Aggressive timelines for product, process and analytical development may be needed, especially in case of disease outbreaks

Development of Control Strategy for Vaccines

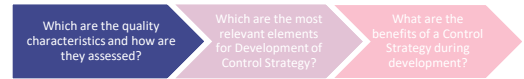


- Control Strategy is instrumental for manufacturing of safe and efficacious products in a robust fashion, and for management of routine manufacturing and analytical changes.
- This presentation will address some key questions, to assess the ability to generate acceptable and consistent values for each Critical Quality Attribute of a vaccine product, with focus on development efforts.



- **Quality characteristics definition**

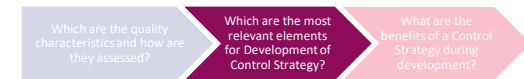
- Approach
- Example of identification and range assessment of an antigen Critical Quality Attribute



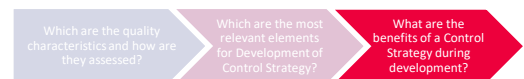
- **Control Strategy development**

Control Strategy and relevance of cross-discipline integration:

- definition of a well- controlled Critical Quality Attribute, examples and possible link with clinical setting
- adjuvant selection

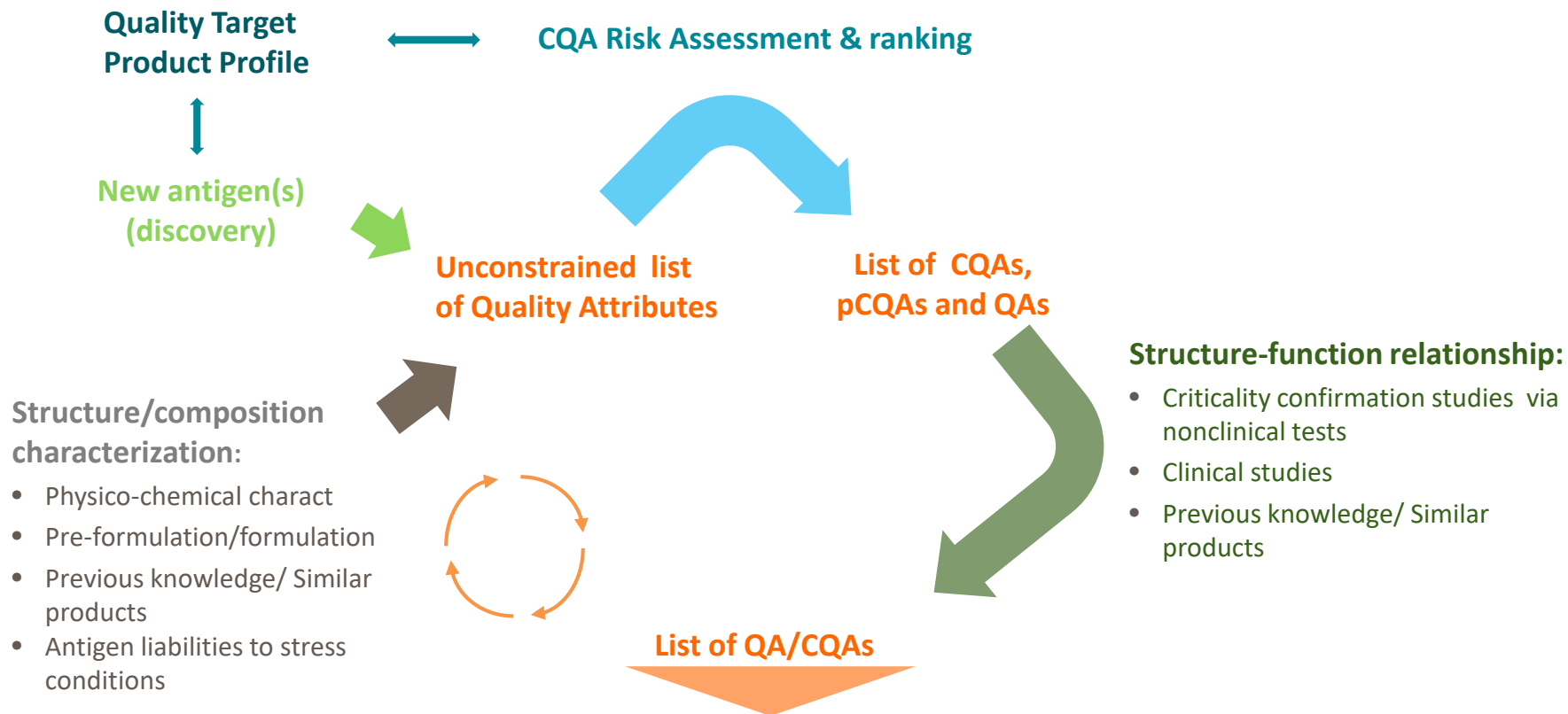


- **Benefits of Control Strategy during development**



Quality characteristics definition

Identification and life cycle of Critical Quality Attributes



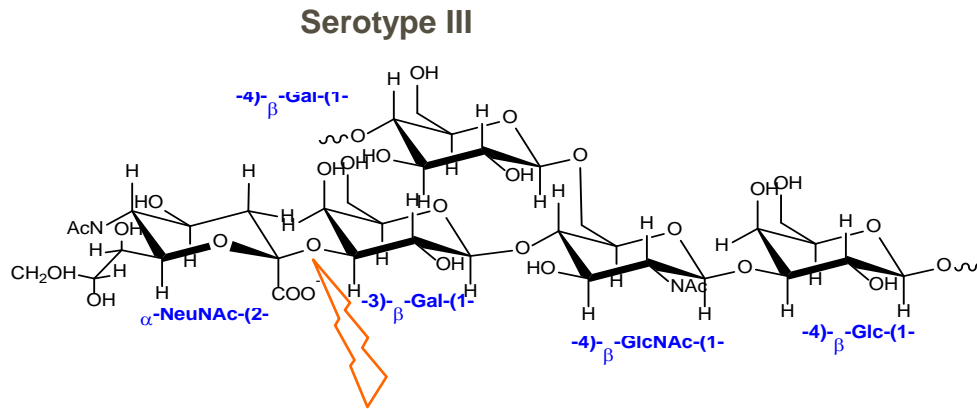
Due to the complexity of vaccines, and to the relatively limited prior/ platform knowledge:

- **New adjuvants/ new structural variants** could be identified during development, **impacting expected dose and activity of a vaccine**
- **Strategy for vaccine strength assessment/ potency testing** typically **evolves as knowledge is gained**

Quality characteristics definition

Structural understanding- Group B streptococcus case study, sialic acid retention

CQA risk assessment



Sialic acid residue is susceptible to hydrolysis; hydrolysis rate depends on temperature and conditions (e.g. pH) → *sialic acid cleavage is a degradation pathway*

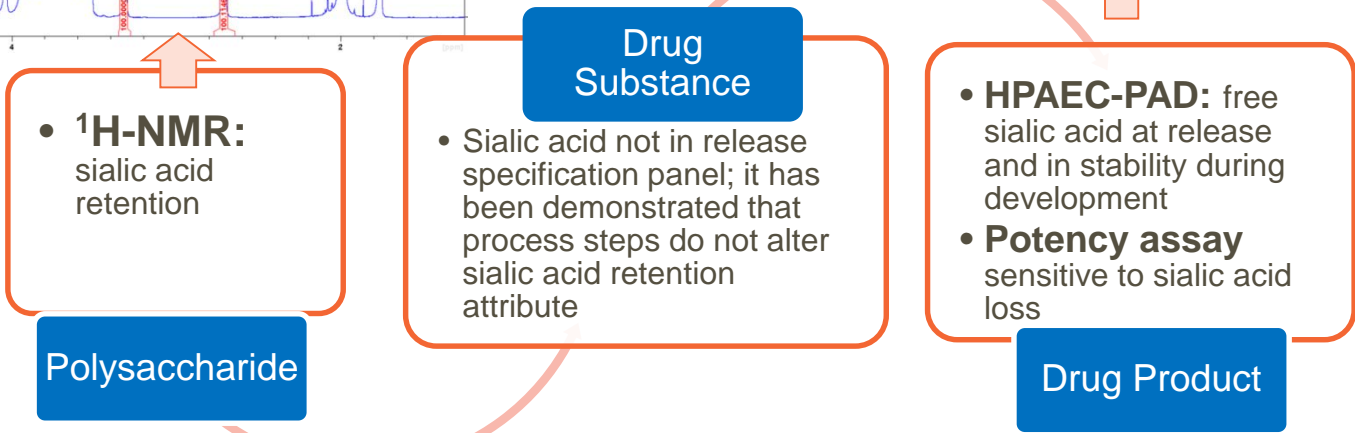
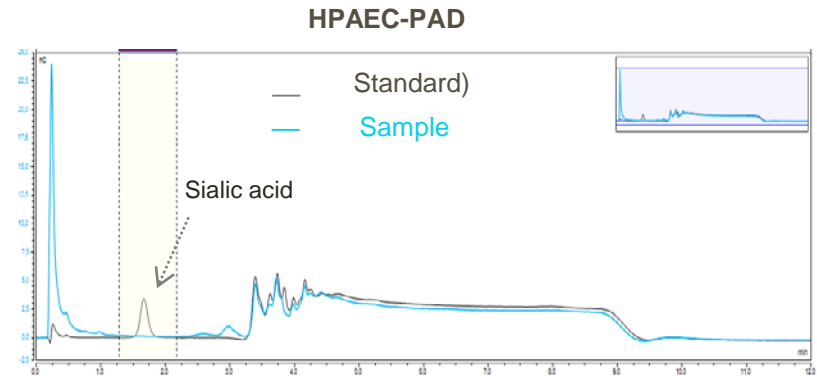
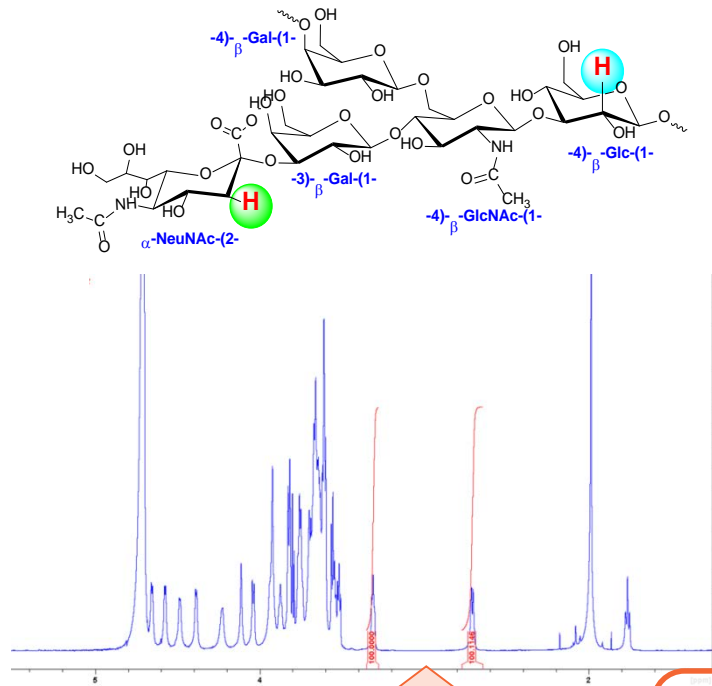
Risk assessment to define Quality Attribute's criticality (evolution depends on uncertainty score)

Quality attribute	Efficacy				Safety				Overall Score		
	Impact	Uncert	Score		Impact	Uncert	Score				
Antigen content	25	Immune response depends on the antigen content	1	Accepted by community	25	2	Not expected to impact safety	1	Accepted by community	2	25
Preservation of terminal sialic acid	25	Immune response dependent on antigen structural integrity	3	Nonclinical studies	75	2	Not expected to impact safety	4	Literature	8	75
Free CRM	2	Immune response not exp to depend on free CRM	4	Literature	8	2	Safety of CRM is proven	1	Accepted by community	2	8



Quality characteristics definition

Analytical Strategy - Group B streptococcus case study, sialic acid retention





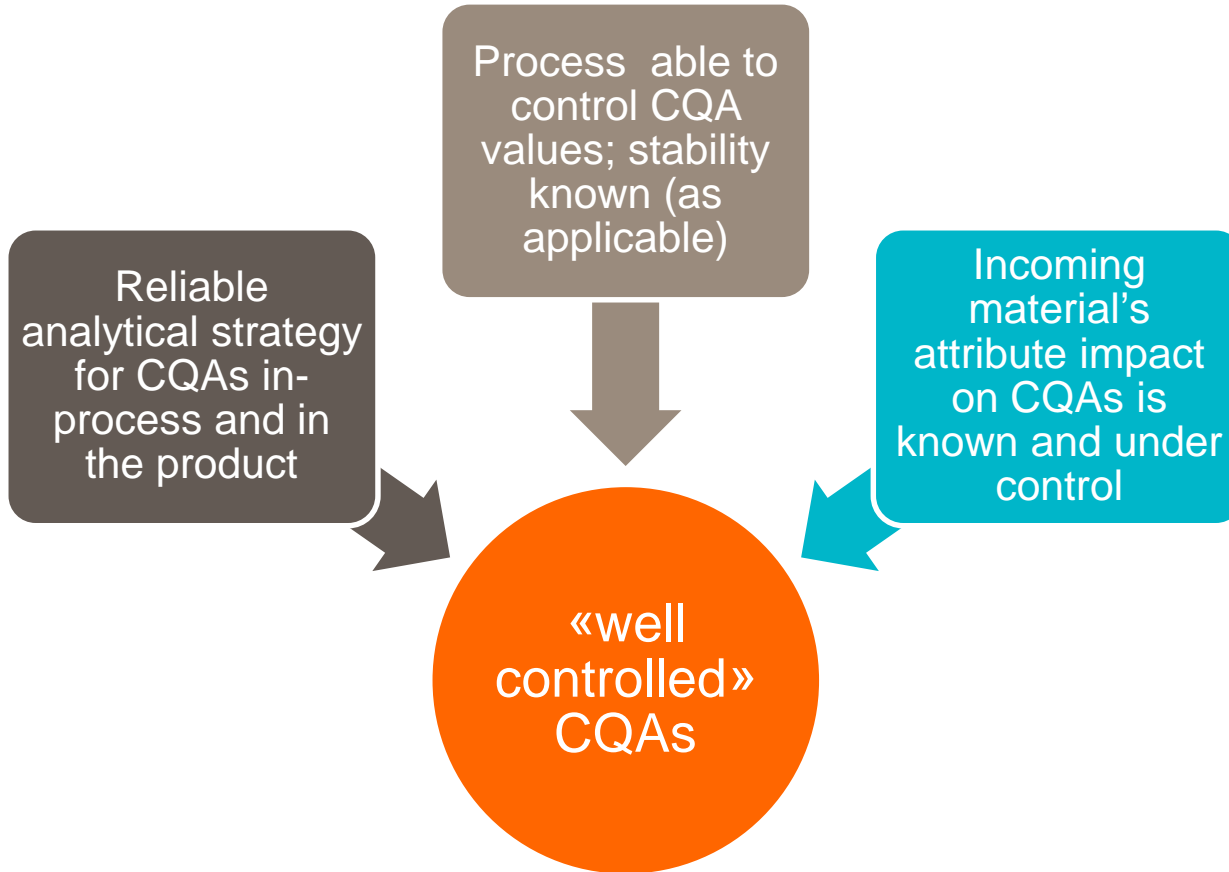
Quality characteristics definition

CQA ranges- Group B streptococcus case study, sialic acid retention

- If correlation between nonclinical and clinical response is missing, **nonclinical studies** are used to increase knowledge on criticality, but **not for setting specification ranges**.
- In these cases, **CQA ranges can be supported by clinical studies with batches reflecting process/ product variability**.
- **Ad hoc clinical exploration of CQA variability is not needed if the CQA is well controlled**. For instance, sialic acid retention range was based on available manufactured lots release & stability data on the basis of the following considerations:
 - The ability of the process to control sialic acid retention (well-controlled and highly conserved attribute)
 - CQA well monitored via suitable analytical tools complying with Analytical Target Profile requirements
 - No increment of free sialic acid observed under real-time and accelerated stability conditions

Control Strategy Development

Defining «well-controlled» CQAs



- Process understanding and analytical studies start focusing on «potential» CQAs
- If (p)CQAs control is achieved early in development, it is possible to use information to prioritize product understanding activities.
- Control Strategy for CQAs is a critical deliverable of overall development, also impacting testing strategy (eg attributes in specification) for commercial product

Control Strategy Development

Defining «well-controlled» CQAs

Critical Quality Attribute expected to be well controlled

Retained sialic acid for some Group B Streptococcus Glycoconjugate serotypes, e.g. Type III (see previous slides) .

Critical Quality Attribute expected to be less well controlled

Degree of Glycosylation of Group B Streptococcus Glycoconjugate (the polysaccharide to protein ratio) can vary depending on the extent of activation of the polysaccharide and reaction parameters of the activated polysaccharide with the carrier protein (e.g., time and temperature).

The question arises as to the basis for setting specifications for the vaccine to encompass this potential lot-to-lot variability during commercial manufacture.



Control Strategy Development

Designing clinical trials supporting product-specific attributes understanding

Clinical studies deliver patient- driven input for commercial lots release and shelf life ranges.



Clinical trials should cover attribute ranges spanning of future commercial lots.



If an attribute is expected to show **varying values due to instability or challenges to control** (manufacturing/ testing), **clinical exploration of maximum variability** should be carried out.



If we **expect a good control of an attribute**, we can use **historical data/ capability considerations** for ranges setting.

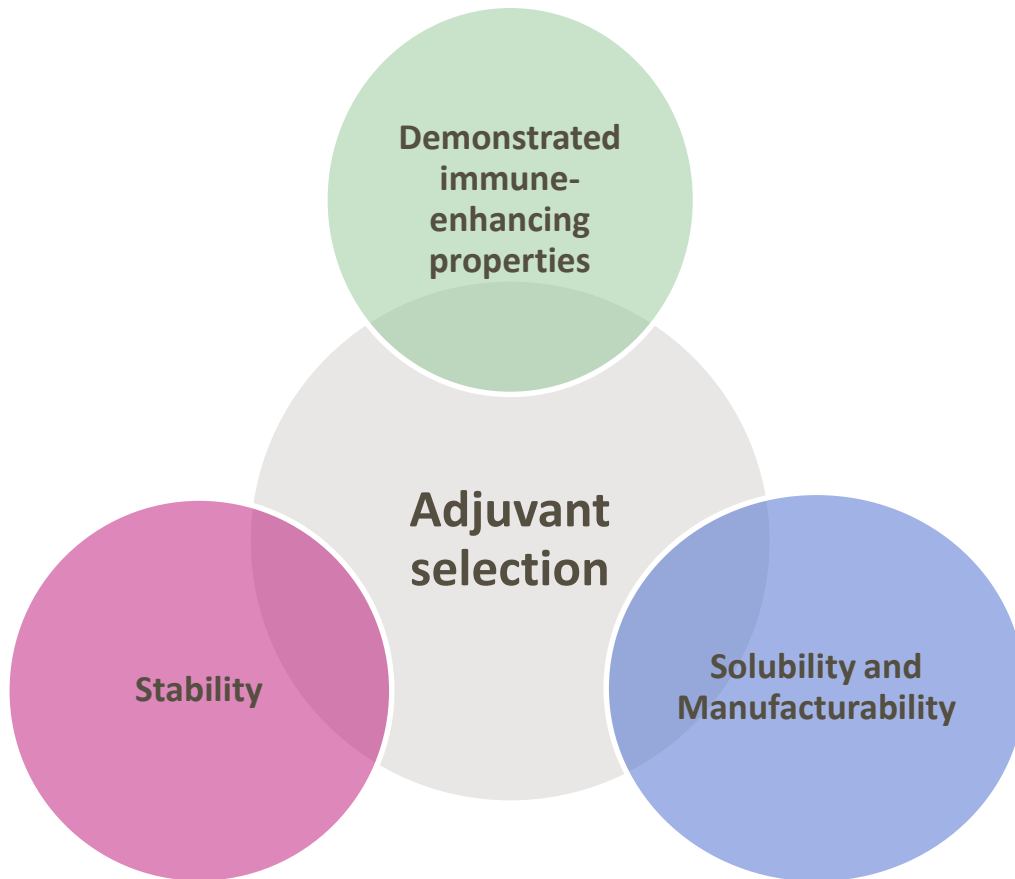
Testing panels (eg specifications, ad hoc characterization, monitoring with internal control limits) should be designed and updated during development, reflecting current knowledge

Control Strategy Development

Additional reflections on Formulation development

Control strategy established as soon as possible supports

- efficient management of drug product composition changes during development
- selection of formulation without neglecting manufacturability considerations.



Adjuvant case studies show

- what can be the triggers for product composition changes and selection of formulation for vaccines
- Importance of cross-disciplinary effort
 - Formulation screening
 - Extensive Physico- chemical characterization
 - Effective testing of immunogenicity
 - Process design and development

Control Strategy Development

Adjuvants - *Malaria and AS03 case studies*

- **Adjuvant** choice has a direct impact on vaccine efficacy and **continued screening** of more effective adjuvants may be needed during development, especially for specific but weakly immunogenic antigens, like **RTS,S** (hybrid antigen in which a portion of the circumsporozoite antigen is fused to hepatitis B surface antigen) for **Malaria**
- **Early and deep antigen understanding** (via **physicochemical** characterization and development of suitable **immunogenicity tests**) as part of early control strategy are critical for supporting Product quality characteristics evolution and related process development
- **Early process requirements definition**, targeting desired product quality, is critical for selection of (new) adjuvants (**AS03 case study**)

Control Strategy Development

Adjuvants changes- *Malaria case study*

AS02

- **Ph I and II** clinical trials with RTS,S/ AS02 demonstrated partial protection against Malaria infection in adults, children and infants

AS01

- Research in mice and rhesus monkeys → AS01 induced significantly superior antigen-specific responses compared to AS02 adjuvant
- Human challenge studies → trend towards better protection
- RTS,S/AS01 was selected for testing in **Phase III** studies.

- **AS02**: oil- water emulsion with 3-deacylated monophosphoryl lipid (MPL) and Quillaja saponaria Molina: fraction 21 (QS-21)
- **AS01**: liposome- based system using MPL and QS-21

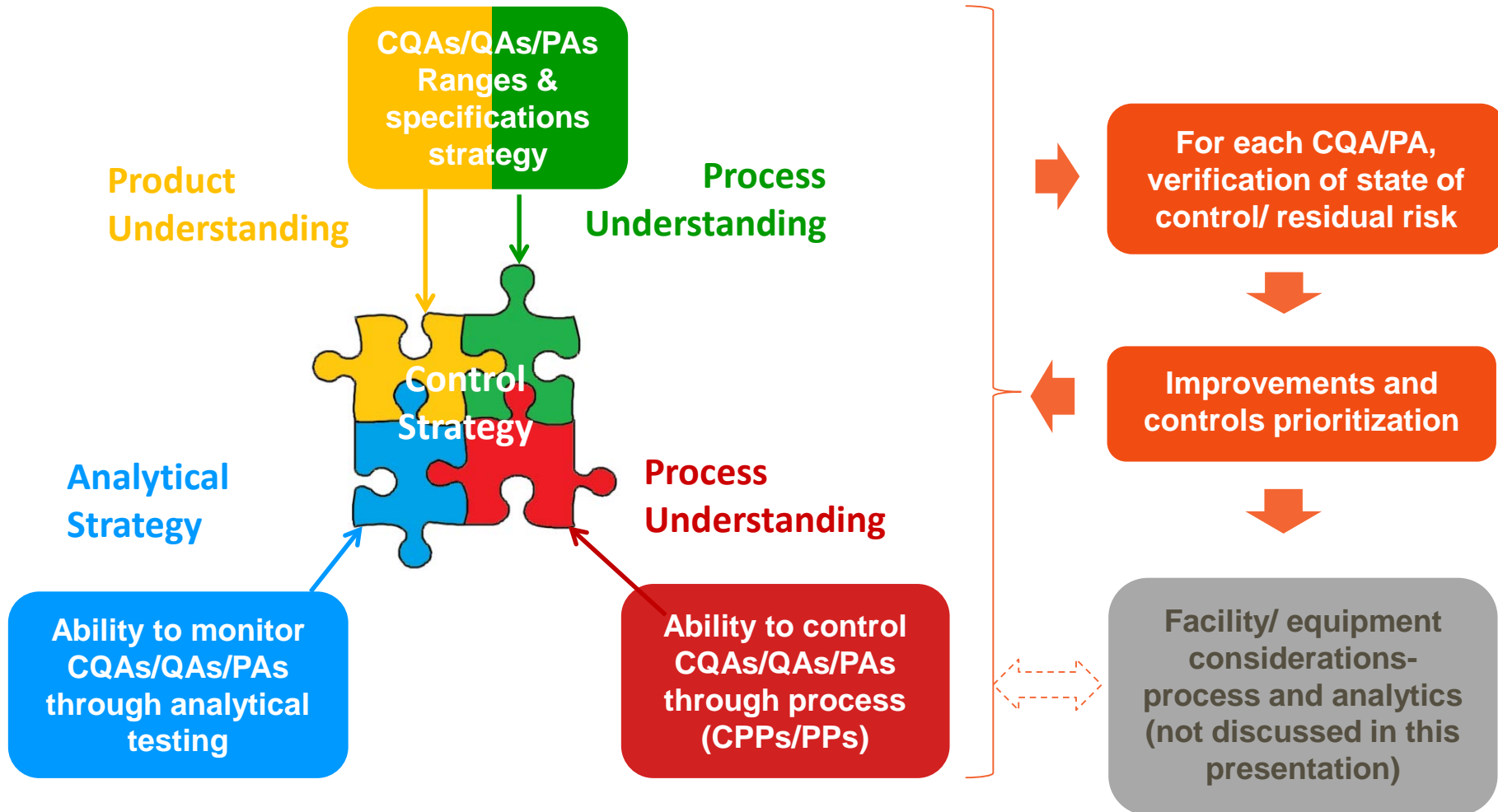
Control Strategy Development

Manufacturability for adjuvant choice - «AS03» Case Study

- «AS03» is an emulsion consisting of squalene and alpha-tocopherol, which has been used for Pandemic H1N1 influenza vaccines.
- **Selection** of this Adjuvant system was the result of extensive screening of oil- in- water emulsions with immune- enhancing properties, targeting
 - Amenability to 0.2 micron **sterile filtration** (to ensure sterility of the final product)
 - **No destabilization** as defined by separation of phases **after** several cycles of **freezing and thawing**

Development of Control Strategy in a QbD perspective

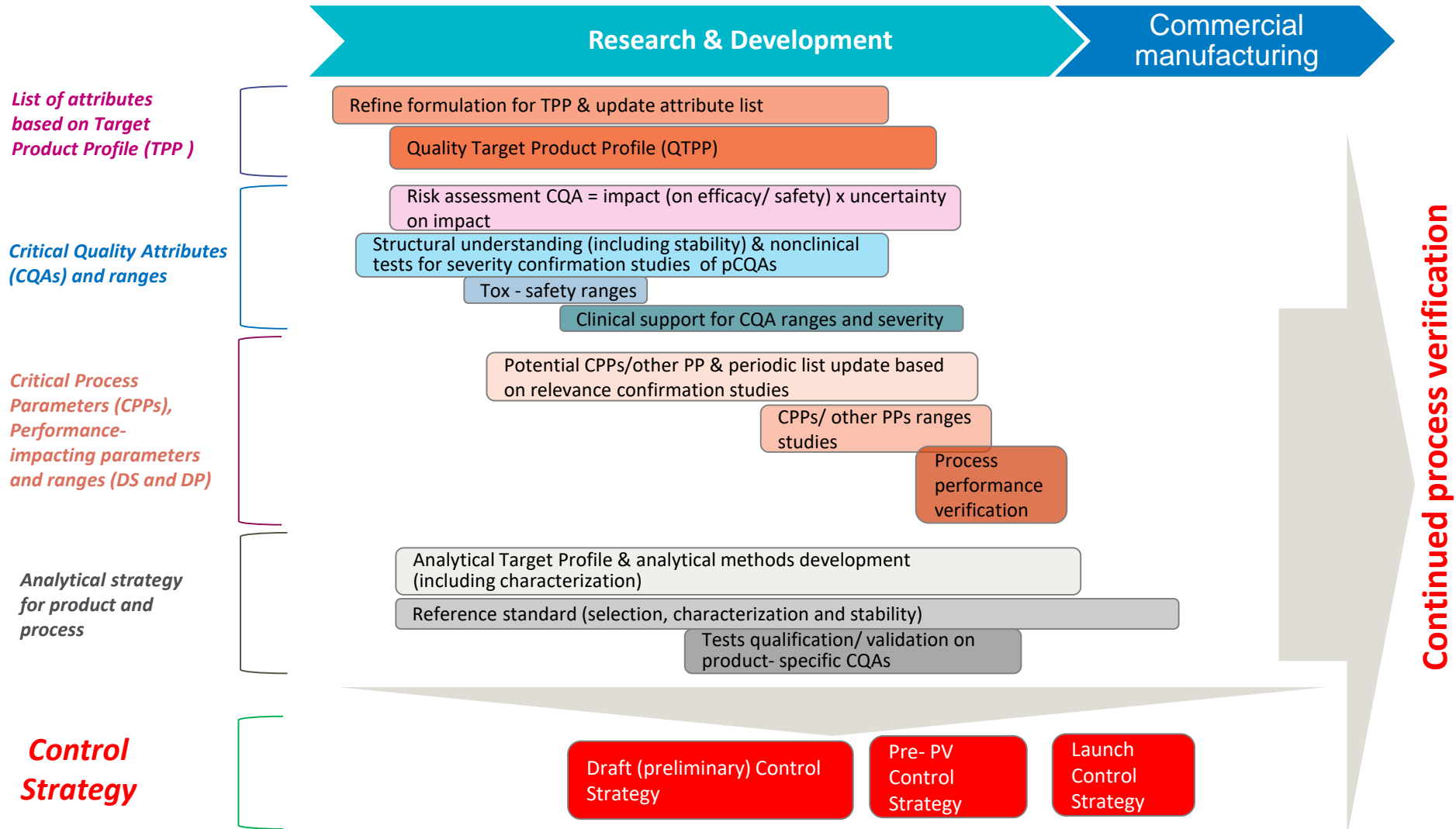
What does it mean, in practice



Development of Control Strategy in a QbD perspective



What does it mean, in practice





Benefits of Control Strategy during development

Control Strategy development based on QbD principles—for Vaccines only?

Supports risk- based decisions for understanding and control of product quality

- CQA assessments, as well as product quality- driven process and analytics, support risk-based prioritization of attributes to be tested in nonclinical and clinical studies

Fosters cross- disciplinary integration and periodic refinement of knowledge

- Activities for product, process and analytical development can be carried out in parallel and deliverables are periodically refined as knowledge is gained/ formulation is optimized
- Early manufacturability assessment may support formulation definition (eg new adjuvant suitability)

Drives focused and structured approach applicable to any vaccine category

- Definition and updates of target for product, process and analytical development enable focus on critical elements.
- Knowledge from other vaccines may be effectively used (as applicable)

Ensures robust grounds for commercial control strategy

- Clear visibility on the extent of product, process and analytical understanding is a critical input for commercial control strategy and sound planning for life cycle management

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Questions?



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